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(54) Title: 11β-SUBSTITUTED PROGESTERONE ANALOGS

(I)
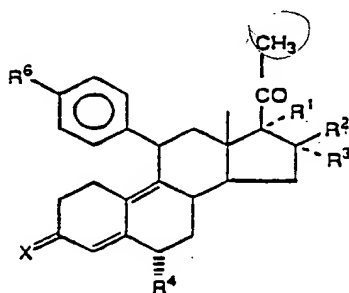
(57) Abstract

An 11β-aryl-19-norprogesterone steroid of formula (I): wherein (i) R^1 is H, C_{1-4} alkyl, C_{2-4} alkenyl, C_{2-4} alkynyl, OH, $OC(O)CH_3$, or $OC(O)R^5$, wherein R^5 is C_{2-8} alkyl, C_{2-8} alkenyl, C_{2-8} alkynyl or aryl, R_2 is H, R^3 is H, C_{1-4} alkyl, C_{2-4} alkenyl or C_{2-4} alkynyl, R^4 is H, CH_3, F or Cl, R^6 is H, $(CH_3)_2N$, CH_3O, CH_3CO, CH_3S, CH_3SO, CH_3SO_2, and X is O or $NOCH_3$; or (ii) R^1 and R^2 taken together are a carbon-carbon bond and R^3, R^4, R^6 and X are as defined above; or (iii) R^1 and R^3 taken together are $-CH_2-$ or $-N=N-CH_2-$, R^2 is H and R^4, R^6 and X are as defined above; or (iv) R^2 and R^3 taken together are $=CH_2$ and R^1, R^4, R^6 and X are as defined above.

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Description
11β -Substituted Progesterone Analogs

Technical Field

This invention relates generally to the field of

5 steroids, and in particular, to new 11β-substituted 19-
norprogesterone analogs which possess
antiprogestational or progestational activity.

Background Art

There have been many prior attempts over the past

10 few decades to prepare steroids with antihormonal
activity. These have been reasonably successful where
anti-estrogens and anti-androgens are concerned. The
discovery of effective antiprogestational and
antiglucocorticoid steroids, however, has proved to be

15 a formidable task for the steroid chemist. It has been
generally recognized for some years, however, that
antiprogestational steroids would find wide
applicability in population control, while
antiglucocorticoids would be extremely valuable in the

20 treatment of, for example, Cushing's syndrome and other
conditions characterized by excessive endogenous
production of cortisone. In the last decade largely
through the efforts of Teutsch et al of the Roussel-
Uclaf group in France, a new series of 19-

25 nortestosterone derivatives has been synthesized with
strong affinity for the progesterone and glucocorticoid
receptors and with marked antiprogestational and
antiglucocorticoid activity in vivo. This important
discovery revealed the existence of a pocket in the

30 progesterone/cortisone receptors able to accommodate a
large 11β-substituent on selected 19-nortestosterone
derivatives. By suitable selection of such a

substituent steroids with antihormonal properties were obtained.

The pioneering studies of Teutsch et al on the synthesis of antiprogestational and antiglucocorticoid
5   steroids is summarized in a recent review (G. Teutsch in Adrenal Steroid Antagonism. Ed. M. K. Agarwal, Walter de Gruyter and Co., Berlin, 1984. pp. 43-75) describing work leading to the discovery of RU-38,486 (I), the first steroid of this type selected for
10   clinical development. See Figure 1. RU-38,486 or mefipristone was found to be an effective antiprogestational/contragestative agent when administered during the early stages of pregnancy (IPPF Medical Bulletin 20; No. 5, 1986). In addition to
15   these antiprogestational properties, mefipristone had very significant antiglucocorticoid activity and was successfully used by Nieman et al (J. Clin. Endocrinology Metab. 61:536, 1985) in the treatment of Cushing's syndrome. In common with the vast majority
20   of steroidal hormone analogs, mefipristone additionally exhibits a range of biological properties. Thus, for example, it exhibits growth-inhibitory properties towards estrogen-insensitive T47Dco human breast cancer cells (Horwitz, Endocrinology 116:2236, 1985).
25   Experimental evidence suggests that the metabolic products derived from mefipristone contribute to its antiprogestational and antiglucocorticoid properties (Heikinheimo et al, J. Steroid Biochem. 26:279, 1987).

There have been a number of attempts by various
30   workers to modify the mefipristone structure in order to obtain separation of the antiprogestational activity from the antiglucocorticoid activity. Thus, the Schering group (Steroids 44:349-519, 1984) has described analogs of mefipristone termed ZK 98.299 (II)

and ZK 98.734 (III).   See Figure 1.   Mefipristone is
the most active antiglucocorticoid steroid relative to
its antigestagenic potency while steroid (III) is the
least active.   Steroid (II) has an intermediate
5 position in this respect.

    Comparison of the contragestative properties of
these three antiprogestational steroids (Elger et al,
J. Steroid Biochem. 25:835, 1986) has not only revealed
different endocrinological profiles, but has indicated
10 the critical importance of the ratio of
antiglucocorticoid to antiprogestational activity to
the biological activity.   It thus seems inevitable that
a series of related structures possessing a gradation
of antiprogestational/antiglucocorticoid properties
15 will need to be developed in order to provide
contragestative/antiglucocorticoid/antitumor products
designed for specific clinical situations.
Unfortunately, the art has not yet reached the stage
when accurate predictions of biological properties on
20 the basis of chemical structures can be made so that a
degree of empiricism is unavoidable.

    There continues to be a need for the development
of new steroids with varying degrees of
antiprogestational and antiglucocorticoid activities.

25   Disclosure of the Invention

    Accordingly, one object of the present invention
is to provide new steroid compounds having anti-
progestational and/or antiglucocorticoidal properties.

    Another object of the invention is to provide
30 novel steroids having progestational as well as
antiprogestational activity.

    These and other objects which will become apparent

from the following specification have been achieved by
the present 11ß-aryl-19-norprogesterone compounds of
the formula
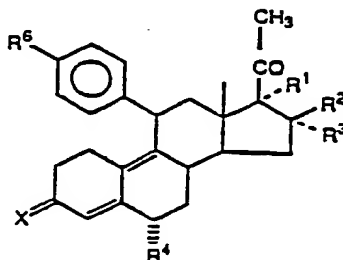
5   wherein (i) R^1 is H, C_{1-4} alkyl, C_{2-4} alkenyl, C_{2-4}
alkynyl, OH, $OC(O)CH_3$, or $OC(O)R^5$, wherein R^5 is C_{2-8}
alkyl, C_{2-8} alkenyl, C_{2-8} alkynyl or aryl, R^2 is H, R^3
is H, C_{1-4} alkyl, C_{2-4} alkenyl or C_{2-4} alkynyl, R^4 is
H, CH_3, F or Cl, R^6 is H, $(CH_3)_2N$, CH_3O, CH_3CO, CH_3S,
10 CH_3SO or CH_3SO_2 and X is O or $NOCH_3$; or (ii) R^1 and R^2
taken together represent a carbon-carbon bond, and R^3,
R^4, R^6 and X are as defined above; or (iii) R^1 and R^3
taken together are $-CH_2-$ or $-N=N-CH_2-$, R^2 is H and R^4,
R^6 and X are as defined above; or (iv) R^2 and R^3 taken
15 together are $=CH_2$ and R^1, R^4, R^6 and X are as defined
above.

Brief Description of the Drawings

A more complete appreciation of the invention and
many of the attendant advantages thereof will be
20 readily obtained as the same becomes better understood
by reference to the following detailed description when
considered in connection with the accompanying
drawings, wherein:

Figure 1 gives the structures of prior art
25 compounds ZK 95.890, ZK 98.734 and ZK 98.299; and

Figure 2 illustrates the structures of the
compounds of the present invention.

Best Mode For Carrying Out the Invention

Research in this area has dealt with 11β-aryl-19-nortestosterone analogs in which the 17β-position (or the 17α-position in the inverted compounds such as III)
5   is substituted by a hydroxyl group. This invention provides for the first time novel 11β-aryl-19-norprogesterone analogs in which the 17β-position is substituted by an acetyl group. The resulting compounds are generally characterized by strong binding
10 affinity to the progesterone and glucocorticoid receptors. Research in this series of structures, however, is not yet able to predict the nature of this biological activity on the basis of structure and binding affinity to the progesterone and glucocorticoid
15 receptors. Thus in contrast to prior art which teaches that in the 11β-aryl-19-nortestosterone series, an 11β-aryl substituent, e.g. 11β-(4-N,N-dimethylaminophenyl), leads to antiprogestational activity, surprisingly in the 11β-aryl-19-norprogesterones of the present
20 invention, strong binding to the progesterone receptor may lead to either antiprogestational or progestational activity in vivo. Thus the 17α-acetoxy structures IV (Figure 2) (R^1 = OAc, $R^2 = R^3$ = H, R^4 = H or CH_3, R^6 = Me_2N, X=O) and the 16α-ethyl structures IV ($R^1 = R^2$ =
25 H, R^3 = Et, R^4 = H or CH_3, R^6 = Me_2N, X=O) both exhibit strong binding to the progesterone receptor. The former compounds block the action of progesterone when administered in vivo, whereas the latter surprisingly show potent progestational activity in vivo.

30   Furthermore in the 19-norprogesterone series there is not always the expected correlation between binding to the progesterone receptor and in vivo activity. Thus the Δ-16 compound IV (R^1,R^2 = double bond, R^3 = R^4 = H, R^6 = Me_2N, X=O) binds relatively weakly to the
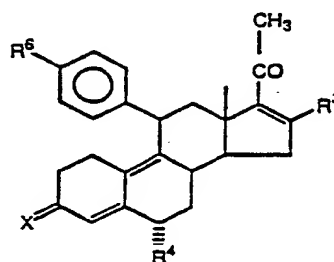
progesterone receptor, but when used in vivo exhibits strong antiprogestational activity.

The 11ß-substituted norprogesterone analogs of the present invention comprise compounds having structures
5   A-C shown below.
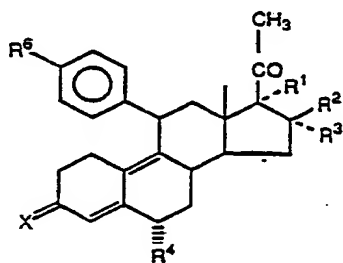
A

B
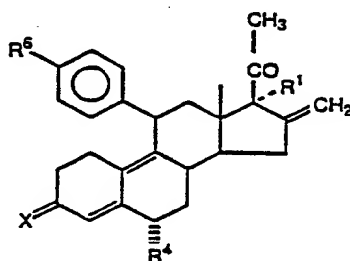
C

The compounds having structure A all contain a 16ß-hydrogen substituent (R^2) and a 17ß -acetyl
10   substituent. The 16α substituent (R^3) may be hydrogen, C_{1-4} alkyl, C_{2-4} alkenyl or C_{2-4} alkynyl groups. The 17α substituent (R^1) may be methyl, C_{2-4} alkyl, C_{2-4} alkenyl, C_{2-4} alkynyl, hydroxyl, $OC(O)CH_3$ (O-acetyl), or $OC(O)R^5$, where R^5 is C_{2-8} alkyl, C_{2-8} alkenyl, C_{2-8}
15   alkynyl or aryl. Alternatively, the 17α- and 16α-

substituents R^1 and R^3 taken together are $-CH_2-$ or
$-N=N-CH_2-$.

Preferred compounds having structure A are those
in which R^6 is N,N-dimethylamino or acetyl. Additional
5   preferred compounds are those in which R^4 is hydrogen
or methyl and R^1 is acetoxy or C_{2-6} alkynyl groups.
Specific examples of compounds having structure A are
17α-acetoxy-6α-methyl-11β-(4-N,N-dimethylaminophenyl)-
19-norpregna-4,9-diene-3,20-dione, 17α-acetoxy-11β-(4-
10 N,N-dimethylaminophenyl)-19-norpregna-4,9-diene-3,20-
dione, 16α-ethyl-11β-(4-N,N-dimethylaminophenyl)-19-
norpregna-4,9-diene-3,20-dione, 16α-ethyl-6α-methyl-
11β-(4-N,N-dimethylaminophenyl)-19-norpregna-4,9-diene-
3,20-dione, 17α-ethynyl-11β-(4-N,N-
15 dimethylaminophenyl)-19-norpregna-4,9-diene-3,20-dione,
11β-(4-N,N-dimethylaminophenyl)-19-norpregna-4,9-diene-
3,20-dione, 11β-(4-acetylphenyl)-19-norpregna-4,9-
diene-3,20-dione, 17α-acetoxy-11β-(4-acetylphenyl)-19-
norpregna-4,9-diene-3,20-dione, and 17α-ethynyl-11β-(4-
20 acetylphenyl)-19-norpregna-4,9-diene-3,20-dione.

Compounds having structure B exhibit a carbon-
carbon double bond between C16 and C17. R^3, R^4, R^6 and
X may be any of the groups defined above. Preferred
compounds having structure B are compounds in which R^6
25 is an N,N-dimethylamino or an acetyl group.
Additionally preferred compounds having structure B are
those in which R^3 is H and R^4 is H or CH_3. Specific
examples of such compounds include 11β-(4-N,N-
dimethylaminophenyl)-19-norpregna-4,9,16-triene-3,20-
30 dione and 11β-(4-acetylphenyl)-19-norpregna-4,9,16-
triene-3,20-dione.

In the compounds having structure C, R^2 and R^3,
taken together, are a $=CH_2$ group. Preferred examples
include compounds in which R^1 is acetoxy or C_{2-8}

alkynyl, R^4 is hydrogen or methyl and R^6 is dimethylamino or acetyl.

Preferred aryl groups for R^5 in compounds A-C have the formula $-C_6H_4-R^6$, in which R^6 has the same meaning as defined above.

Steroids having progestational, antiprogestational and/or antiglucocorticoid activity have use in the control of fertility in humans and non-human mammals such as primates, domestic pets and farm animals, and in the treatment of medical conditions in animals or humans in which these activities are beneficial. Thus they may be useful in the treatment of conditions such as Cushing's syndrome, glaucoma, endometriosis, premenstrual syndrome and cancer in addition to their use in the control of reproduction.

The compounds of the present invention may be administered by a variety of methods. Thus, those products of the invention that are active by the oral route may be administered in solutions, suspensions, emulsions, tablets, including sublingual and intrabuccal tablets, soft gelatin capsules, including solutions used in soft gelatin capsules, aqueous or oil suspensions, emulsions, pills, lozenges, troches, tablets, syrups or elixirs and the like. Products of the invention active on parenteral administration may be administered by depot injection, implants including Silastic™ and biodegradable implants, intramuscular and intravenous injections.

Compositions may be prepared according to any method known to the art for the manufacture of pharmaceutical compositions and such compositions may contain one or more agents selected from the group consisting of sweetening agents, flavoring agents,

coloring agents and preserving agents. Tablets
containing the active ingredient in admixture with
nontoxic pharmaceutically acceptable excipients which
are suitable for manufacture of tablets are

5   acceptable. These excipients may be, for example,
inert diluents, such as calcium carbonate, sodium
carbonate, lactose, calcium phosphate or sodium
phosphate; granulating and disintegrating agents, such
as maize starch, or alginic acid; binding agents, such

10 as starch, gelatin or acacia; and lubricating agents,
such as magnesium stearate, stearic acid or talc.
Tablets may be uncoated or may be coated by known
techniques to delay disintegration and adsorption in
the gastrointestinal tract and thereby provide a

15 sustained action over a longer period. For example, a
time delay material such as glyceryl monostearate or
glyceryl distearate alone or with a wax may be
employed.

Formulations for oral use may also be presented as
20 hard gelatin capsules wherein the active ingredient is
mixed with an inert solid diluent, for example calcium
carbonate, calcium phosphate or kaolin, or as soft
gelatin capsules wherein the active ingredient is mixed
with water or an oil medium, such as peanut oil, liquid
25 paraffin or olive oil.

Aqueous suspensions of the invention contain the
active materials in admixture with excipients suitable
for the manufacture of aqueous suspensions. Such
excipients include a suspending agent, such as sodium
30 carboxymethylcellulose, methylcellulose, hydroxypropyl-
methylcellulose, sodium alginate, polyvinylpyrrolidone,
gum tragacanth and gum acacia, and dispersing or
wetting agents such as a naturally occurring
phosphatide (e.g., lecithin), a condensation product of

an alkylene oxide with a fatty acid (e.g.,
polyoxyethylene stearate), a condensation product of
ethylene oxide with a long chain aliphatic alcohol
(e.g., heptadecaethylene oxycetanol), a condensation
5   product of ethylene oxide with a partial ester derived
from a fatty acid and a hexitol (e.g., polyoxyethylene
sorbitol mono-oleate), or a condensation product of
ethylene oxide with a partial ester derived from fatty
acid and a hexitol anhydride (e.g., polyoxyethylene
10 sorbitan mono-oleate). The aqueous suspension may also
contain one or more preservatives such as ethyl or n-
propyl p-hydroxybenzoate, one or more coloring agents,
one or more flavoring agents and one or more sweetening
agents, such as sucrose, aspartame or saccharin.
15 Ophthalmic formulations, as is known in the art, will
be adjusted for osmotic pressure.

    Oil suspensions may be formulated by suspending
the active ingredient in a vegetable oil, such as
arachis oil, olive oil, sesame oil or coconut oil, or
20 in a mineral oil such as liquid paraffin. The oil
suspensions may contain a thickening agent, such as
beeswax, hard paraffin or cetyl alcohol. Sweetening
agents may be added to provide a palatable oral
preparation. These compositions may be preserved by
25 the addition of an antioxidant such as ascorbic acid.

    Dispersible powders and granules of the invention
suitable for preparation of an aqueous suspension by
the addition of water may be formulated from the active
ingredients in admixture with a dispersing, suspending
30 and/or wetting agent, and one or more preservatives.
Suitable dispersing or wetting agents and suspending
agents are exemplified by those disclosed above.
Additional excipients, for example sweetening,
flavoring and coloring agents, may also be present.

The pharmaceutical compositions of the invention
may also be in the form of oil-in-water emulsions. The
oily phase may be a vegetable oil, such as olive oil or
arachis oil, a mineral oil, such as liquid paraffin, or
5   a mixture of these. Suitable emulsifying agents
include naturally-occurring gums, such as gum acacia
and gum tragacanth, naturally occurring phosphatides,
such as soybean lecithin, esters or partial esters
derived from fatty acids and hexitol anhydrides, such
10   as sorbitan mono-oleate, and condensation products of
these partial esters with ethylene oxide, such as
polyoxyethylene sorbitan mono-oleate. The emulsion may
also contain sweetening and flavoring agents.

Syrups and elixirs may be formulated with
15   sweetening agents, such as glycerol, sorbitol or
sucrose. Such formulations may also contain a
demulcent, a preservative, a flavoring or a coloring
agent.

The pharmaceutical compositions of the invention
20   may be in the form of a sterile injectable preparation,
such as a sterile injectable aqueous or oleaginous
suspension. This suspension may be formulated
according to the known art using those suitable
dispersing or wetting agents and suspending agents
25   which have been mentioned above. The sterile
injectable preparation may also be a sterile injectable
solution or suspension in a nontoxic parenterally-
acceptable diluent or solvent, such as a solution of
1,3-butanediol. Among the acceptable vehicles and
30   solvents that may be employed are water and Ringer's
solution, an isotonic sodium chloride. In addition,
sterile fixed oils may conventionally be employed as a
solvent or suspending medium. For this purpose any
bland fixed oil may be employed including synthetic

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mono- or diglycerides. In addition, fatty acids such
as oleic acid may likewise be used in the preparation
of injectables.

5 The compounds of this invention may also be
administered in the form of suppositories for rectal
administration of the drug. These compositions can be
prepared by mixing the drug with a suitable non-
irritating excipient which is solid at ordinary
temperatures but liquid at the rectal temperatures and
10 will therefore melt in the rectum to release the
drug. Such materials are cocoa butter and polyethylene
glycols.

They may also be administered by intranasal,
intraocular, intravaginal, and intrarectal routes
15 including suppositories, insufflation, powders and
aerosol formulations.

Products of the invention which are preferably
administered by the topical route may be administered
as applicator sticks, solutions, suspensions,
20 emulsions, gels, creams, ointments, pastes, jellies,
paints, powders, and aerosols.

Products having anti-glucocorticoid activity are
of particular value in pathological conditions
characterized by excess endogenous glucocorticoid such
25 as Cushing's syndrome, hirsutism and in particular when
associated with the adrenogenital syndrome, ocular
conditions associated with glucocorticoid excess such
as glaucoma, stress symptoms associated with excess
glucocorticoid secretion and the like.

30 Products having progestational activity are of
particular value as progestational agents, ovulation
inhibitors, menses regulators, contraceptive agents,
agents for synchronization of fertile periods in

cattle, endometriosis, and the like. When used for
contraceptive purposes, they may conveniently be
admixed with estrogenic agents, such as for example as
ethynylestradiol or estradiol esters.

5   Products having anti-progestational activity are
characterized by antagonizing the effects of
progesterone. As such, they are of particular value in
control of hormonal irregularities in the menstrual
cycle and for synchronization of fertile periods in
10 cattle.

The compounds of the invention may be used for
control of fertility during the whole of the
reproductive cycle. They are of particular value as
postcoital contraceptives, for rendering the uterus
15 inimical to implantation, and as "once a month"
contraceptive agents. They may be used in conjunction
with prostaglandins, oxytocics and the like.

A further important utility for the products of
the invention lies in their ability to slow down growth
20 of hormone-dependent cancers. Such cancers include
kidney, breast, endometrial, ovarian cancers, and
prostate cancer which are characterized by possessing
progesterone receptors and may be expected to respond
to the products of this invention. Other utilities of
25 anti-progestational agents include treatment of
fibrocystic disease of the breast. Certain cancers and
in particular melanomas may respond favorably to
corticoid/anticorticoid therapy.

The compounds according to the present invention
30 may be administered to any warm-blooded mammal such as
humans, domestic pets, and farm animals. Domestic pets
include dogs, cats, etc. Farm animals include cows,
horses, pigs, sheep, goats, etc.

The amount of active ingredient that may be combined with a carrier material to produce a single dosage form will vary depending upon the disease treated, the mammalian species, and the particular mode
5 of administration. For example, a unit dose of the steroid may preferably contain between 0.1 milligram and 1 gram of the active ingredient. A more preferred unit dose is between 0.001 and 0.5 grams. It will be understood, however, that the specific dose level for
10 any particular patient will depend on a variety of factors including the activity of the specific compound employed; the age, body weight, general health, sex and diet of the individual being treated; the time and route of administration; the rate of excretion; other
15 drugs which have previously been administered; and the severity of the particular disease undergoing therapy, as is well understood by those of skill in the art.

Other features of the invention will become apparent in the course of the following descriptions of
20 exemplary embodiments which are given for illustration of the invention and are not intended to be limiting thereof.

EXAMPLES

Example 1. Synthesis of 6α-Methyl-17α-acetoxy-11β-(4-
25 N,N-dimethylaminophenyl)-19-norpregna-4,9-diene-3,20-dione.

6α-Methyl-17α-hydroxy-pregna-1,4-diene-3,20-dione (37.72 g, 0.11 mol) was dissolved in 1 L of freshly distilled tetrahydrofuran and 400 mL of dry methanol.
30 The solution was cooled in an ice-bath at 0°C. Sodium borohydride (3.6 g, 0.09 mol) was added in one portion and the mixture was stirred at 0-5°C for 6 h. The

reaction mixture was diluted with ice water (100 mL)
and methanol was removed under reduced pressure. The
resulting thick residue was partitioned between
chloroform and water. The chloroform extracts

5 (500 mL x 4) was dried over Na_2SO_4 (anhydrous),
filtered and concentrated to give 42 g of crude 6α-
methyl-17α,20β(α)- dihydroxy-pregna-1,4-dien-3-one. The
product was shown to be a mixture of 20β and 20α-ol in
a ratio of 85:15 based on ^{1}H NMR analysis. For 20β-

10 ol: ^{1}H NMR ($CDCl_3$, 60 MHz) δ 0.83 (s, 3, 18-CH_3), 1.0
(d, 3, J = 6 Hz, 6-CH_3), 1.18 (d, 3, J = 6 Hz, 21-CH_3),
4.0 (m, 1, 20-H), 6.05 (bs, 1, 4-H), 6.15 (dd, 1, J =
12, 2 Hz, 2-H), 7.1 (d, 1, J = 12 Hz, 1-H).

Into a flame dried 2 L three-neck round bottom

15 flask equipped with condenser and addition funnel were
added tetrahydrofuran (900 mL), biphenyl (45 g, 0.29
mol) and diphenylmethane (50 mL, 0.285 mol). The
mixture was heated to reflux and lithium wire (3.5 g,
0.50 mol) was added in one portion. The resulting

20 bluish-green solution of the complex was heated at
gentle reflux for 16 h. An additional 0.5 g of lithium
wire was added to maintain a dark-blue color. The diol
(26 g, 0.076 mol) in 170 mL of THF was then added
dropwise at such a rate that the blue color persisted

25 throughout the addition. The reaction mixture was
refluxed for an additional 45 min. The excess biphenyl
lithium complex was quenched carefully with methanol in
an ice-bath. After dilution with water (200 mL), THF
was removed under reduced pressure and the product was

30 extracted with $CHCl_3$ (500 mL x 3). The $CHCl_3$ extracts
were combined, dried over sodium sulfate (anhydrous),
filtered and concentrated to give 118 g of the crude
product. The aqueous phase was acidified with HCl
solution (10% v/v) and extracted with $CHCl_3$ (500 mL x

2). The CHCl$_3$ extract was dried over Na$_2$SO$_4$ (anhydrous), filtered and concentrated to give 4.5 g of fairly pure 6α-methyl-19-norpregna-1,3,5(10)-triene-3,17α,20β(α)-triol. The 118 g of crude reaction product was purified by SiO$_2$ column chromatography employing a gradient system (n-hexane-CH$_2$Cl$_2$ to 5% acetone-CH$_2$Cl$_2$) to give another 11.2 g of the product: mp=175-179°C; ^{1}H NMR (250 MHz, CDCl$_3$) δ 0.82 (s, 3, 18-CH$_3$), 1.17 (d, 3, J = 6.4 Hz, 21-CH$_3$), 1.28 (d, 3, J = 6.8 Hz, 6α-CH$_3$), 4.0 (m, 1, 20-H), 6.61 (dd, 1, J=8.5, 2.6 Hz, 2-H), 6.76 (d, 1, J = 2.6 Hz, 4-H), 7.11 (d, 1, J = 8.5 Hz, 1-H); calcd. mass for C$_{21}$H$_{30}$O$_3$: 330,2095, Found: 330.2197.

Anal. Calcd for C$_{21}$H$_{30}$O$_3$: C. 76.32; H. 9.15. Found: C, 76.82; H, 9.40.

The above crude phenolic product (6.5 g, 0.02 mol) was dissolved in 500 mL of methanol and treated with potassium carbonate (15.0 g, 0.10 mol) and iodomethane (20 mL, 0.32 mol). The mixture was stirred at room temperature for 48 hours. Methanol was removed under reduced pressure, the residue was diluted with water and acidified with 10% (v/v) HCl solution. The product was extracted with CHCl$_3$ (300 mL x 3). The combined CHCl$_3$ extract was washed with water, dried over sodium sulfate (anhydrous), filtered and concentrated to give 7.0 g of crude reaction product. SiO$_2$ column chromatography (CH$_2$Cl$_2$ to 5% acetone-CH$_2$Cl$_2$) gave three fractions: Fraction A (4.0 g) was found to be 6α-methyl-3-methoxy-19-norpregna-1,3,5(10)-triene-17α,20β(α)- diol. Fraction B (0.74 g) was found to be its 20α-hydroxy isomer and Fraction C (0.54 g) was the recovered starting phenol. For the 20β-ol: mp=145-147°C; ^{1}H NMR (250 MHz, CDCl$_3$) δ 0.82 (s, 3, 18-CH$_3$), 1.20 (d, 3, J = 6.3 Hz, 21-CH$_3$), 1.30 (d, 3, J = 7.0

Hz, 6α-CH$_3$), 2.79 (s, 3, OCH$_3$, 4.06 (m, 1, 20-H), 6.73
(dd, 1, J = 8.7, 2.7 Hz, 2-H), 6.82 (d, 1, J = 2.7 Hz,
4-H), 7.20 (d, 1, J = 8.7 Hz, 1-H); Calcd mass for
C$_{22}$H$_{32}$O$_3$: 344.2355. Found 344.2355. Anal. Calcd for
C$_{22}$H$_{32}$O$_3$: C, 77.16; H, 8.83. Found: C, 77.14: H,
8.88. For 20α-ol: mp=150-151°C; ^{1}H NMR (250 MHz,
CDCl$_3$) δ 0.75 (s, 3, 18-CH$_3$), 1.22 (d, 3, J = 6.4 Hz,
21-CH$_3$), 1.30 (d, 3, J = 6.9 Hz, 6α-CH$_3$), 3.79 (s, 3,
OCH$_3$), 3.85 (m, 1, 20-H), 6.70 (dd, J = 8.7, 2.7 Hz, 2-
H), 6.82 (d, 1, J = 2.7 Hz, 4-H), 7.20 (d. 1. J = 8.6
Hz, 1-H).

Liquid ammonia (35 mL) was condensed into a flame
dried three-neck round bottom flask equipped with a
Dewar condenser and an additional funnel. Lithium wire
(150 mg, 21.6 mmol) was added and the resulting bluish
solution of the Li/NH$_3$ complex solution was stirred at
-78°C for 1 hour. The above methyl ether (380 mg. 1.11
mmol) in 2.0 mL of dry THF and 1.0 mL of t-butanol was
added dropwise. The blue color persisted throughout
the addition. The resulting mixture was stirred at
-78°C for an additional 45 minutes and quenched
carefully with methanol until the blue color faded.
Excess ammonia was evaporated under a slow stream of
nitrogen. The residue was diluted with water and
neutralized with 10% (v/v) HCl solution. The product
was extracted with CHCl$_3$ (50 mL x 3). The CHCl$_3$
extract was dried over Na$_2$SO$_4$ (anhydrous), filtered and
concentrated to give 380 mg of crude 6α-methyl-3-
methoxy-19-norpregna-2,5(10)-diene-17α,20β-diol. ^{1}H
NMR (60 MHz) δ 0.80 (s, 3, 18-CH$_3$), 1.0 (d, 3, J = 6.4
Hz, 6α-CH$_3$), 1.2 (d, J = 6 Hz, 21-CH$_3$), 3.5 (s, 3, 3-
OCH$_3$), 4.0 (m, 1, 20-H), 4.6 (bs, 1, 2-h).

Without further purification the crude Birch
reduction product was dissolved in 40 mL of methanol

and treated with oxalic acid (250 mg in 1.5 mL of
H_2O). The mixture was stirred at room temperature for
5 hours and then solvent removed under pressure and the
product extracted with $CHCl_3$ (50 mL x 3). The $CHCl_3$
5 extract was dried over Na_2SO_4 (anhydrous), filtered and
concentrated to give 350 mg of the crude hydrolyzed
product. Column chromatography (SiO_2; gradient from
CH_2Cl_2 to 5% acetone CH_2Cl_2) gave 120 mg of 6α-methyl-
17α,20β-dihydroxy-19-norpregn-5(10)-en-3-one: ^{1}H NMR
10 (250 MHz, $CDCl_3$) δ 0.82 (s, 3, 18-CH_3), 0.99 (d, 3, J =
6.9 Hz, 6α-CH_3, 1.18 (d, 3, J = 6.2 Hz, 21-CH_3), 2.4
(bs, 2, 4-H), 4.0 (m, 1, 20-H).

Purified 6α-methyl-17α,20β-dihydroxy-19-norpregna-
5(10)-en-3-one (8.31 g, 0.025 mol) in 450 mL of dry
15 pyridine was cooled in an ice bath and treated with
pyridinium hydrobromide perbromide (9.30 g, 0.028
mol). After the mixture was stirred at room
temperature for 24 hours, it was poured into ice-cold
sodium sulfite solution (500 mL, 10% w/v) and extracted
20 with $CHCl_3$ (400 mL x 3). The $CHCl_3$ extract was washed
with dilute $NaHCO_3$ solution (5% w/v), dried over Na_2SO_4
(anhydrous), filtered and concentrated to give 8.5 g of
crude reaction product. Column chromatography (SiO_2;
gradient from CH_2Cl_2 to 5% acetone in CH_2Cl_2) gave 5.8
25 g of 6α-methyl-17α,20β-dihydroxy-19-norpregna-4,9-dien-
3-one: mp=201-203°C; ^{1}H NMR (250 MHz, $CDCl_3$), δ 0.97
(s, 3, 18-CH_3); 1.13 (d, J = 6.5 Hz, 6α-CH_3), 1.19 (d,
3, J = 6.2 Hz, 21-CH_3), 4.08 (m, 1, 20-H), 5.8 (bs, 1,
4-H), IR ($CHCl_3$) 3550-3400; (-OH), 1665 (conjugated
30 3-C=O) cm^{-1}; UV (MeOH) λ_{max} 305 nm; MS Calcd mass for
$C_{21}H_{30}O_3$ 330.2195; Found 330.2194; Anal. Calcd for
$C_{21}H_{30}O_3$; C, 76.33; H, 9.15. Found: C, 76.35; H,
9.17.

To a stirred solution of CH_2Cl_2 (150 ml) and

oxalyl chloride (4.5 mL, 0.050 mol) was added DMSO (9.0
mL, 0.12 mol) at -60°C in a dry ice-CHCl$_3$ bath. The
mixture was stirred for 5 min and the above compound
(5.7 g, 0.017 mol) in 60 mL of methylene chloride was

5 added during 5 min; stirring was continued for an
additional 30 min. Triethylamine (25 mL, 0.175 mol)
was added and the reaction mixture was stirred for 15
min and then allowed to warm briefly to room
temperature. Water (150 mL) was then added and the

10 aqueous layer was reextracted with CH$_2$Cl$_2$ (300 mL x
2). The organic layers were combined, washed with
saturated NaCl solution, dried, filtered and
concentrated to give 5.8 g of crude reaction product.
Column chromatography (SiO$_2$; CH$_2$Cl$_2$ → 10% acetone in

15 CH$_2$Cl$_2$) provided 5.1 g of 6α-methyl-17α-hydroxy-19-
norpregna-4,9(10)-diene-3,20-dione. Recrystallization
from MeOH gave white crystals: mp=230-232°C; ^{1}H NMR
(CDCl$_3$, 60 MHz) δ 0.78 (s, 3, 18-CH$_3$), 1.10 (d, 3, J =
6.5 Hz, 6α-CH$_3$), 2.25 (s, 3, 21-CH$_3$), 5.85 (bs, 1, 4-

20 H), IR (CHCl$_3$) 1700 (20-C=O), 1665 (conjugated 3-C=O)
cm^{-1}; UV (MeOH) λ_{max} 305 nm; Calcd mass for C$_{21}$H$_{28}$O$_3$:
328.2038. Found: 328.2038; Anal. Calcd for
C$_{21}$H$_{28}$O$_3$: C, 76.79; H, 8.59. Found: C, 76.87; H,
8.64.

25   To a solution of the above dione (5.8 g, 0.018
mol) in 450 mL of dry benzene was added ethylene glycol
(24.0 mL) and p-toluenesulfonic acid (500 mg). The
mixture was heated to reflux and a total of 150 mL of
benzene was distilled off over a period of 3 h. The

30 reaction mixture was poured over ice water and
extracted with ethyl acetate (300 mL x 3). The organic
phase was washed with water, dried over sodium sulfate
(anhydrous), filtered and concentrated. The crude
residue was chromatographed over SiO$_2$ (100% CH$_2$Cl$_2$ → 2%

acetone-CH_2Cl_2) to give 4.6 g of 6α-methyl-3,3,20,20-
bis-(ethylenedioxy)-19-norpregna-5(10),9(11)-dien-17α-
ol together with 1.0 g of 6β-methyl-3,3,20,20-bis-
(ethylenedioxy)-19-norpregna-5(10),9(11)-dien-17α-ol.

5   For the 6α-methyl-3,20-diketal: mp=157-158°C; ^{1}H NMR
(CDCl₃, 250 MHz) δ 0:78 (s, 3, 18-CH₃); 0.99 (d, 3, J =
6.8 Hz, 6α-CH₃), 1.37 (s, 3, 21-CH₃), 3.98 (m, 8,
3,3,20,20-bisketals), 5.57 (bs, 1, 11-H), Calcd mass
for $C_{25}H_{36}O_5$: 416.2563. Found 416.2564; Anal. Calcd
10   for $C_{25}H_{36}O_5$: C, 72.08; H, 8.71. Found: C, 72.14; H,
8.75.

To a solution of the above bisketal (3.2 g, 7.7
mmol) in 75 mL of methylene chloride/hexane (1:3) was
added m-chloroperbenzoic acid (1.62 g, 80%) at 0°C.
15   The mixture was stirred at 0°C for 10 min and then
diluted with sodium bicarbonate solution (25 mL, 5%
w/v). The aqueous phase was extracted with CH_2Cl_2 (50
mL x 2). The combined organic phase was washed with
saturated sodium chloride solution, dried over sodium
20   sulfate (anhydrous), filtered and concentrated to give
3.4 g of crude epoxides which consisted mainly of
5α,10α-epoxide as revealed by TLC and ^{1}H NMR
analyses: ^{1}H NMR (CDCl₃, 60 MHz) δ 0.75 (s, 3, 18-
CH₃), 0.95 (d, 3, J = 6.0 Hz, 6α-CH₃), 1.30 (s, 3, 21-
25   CH₃), 3.8-4.0 (m, 8, 3, 20-ketals), 5.8 (m, 1, 11-H).

The crude epoxide (3.4 g, 7.43 mmol) in dry
tetrahydrofuran (25 mL) was added dropwise to a
Grignard solution of p-N,N-dimethylaminophenylmagnesium
bromide in the presence of dimethylsulfide cuprous
30   bromide complex (1.8 g. 8.6 mmol). The Grignard
mixture was prepared from p-bromo-N,N-dimethylaniline
(14.0 g, 70 mmol) and magnesium (1.4 g, 57 mmol) in 150
mL of freshly distilled tetrahydrofuran. After the
reaction mixture was stirred at room temperature and

under nitrogen for 30 min., it was poured into
saturated ammonium chloride solution (350 mL) and
stirred for 20 min. Extraction with ethyl acetate (500
mL x 3) and evaporation of the solvent gave a bluish
5   residue which was first purified by Al_2O_3 column
chromatography to provide 3.7 g of semi-purified
product. Repeated silica gel column chromatography
yielded 1.95 g of 6α-methyl-11β-(4-N,N-
dimethylaminophenyl)-3,3,20,20-bis(ethylenedioxy)-19-
10 norpregn-9-en-5α-ol. Recrystallization from
MeOH/CH_2Cl_2 gave 1.2 g of needles: mp=227-228°C; [1]H
NMR (250 MHz, $CDCl_3$) δ 0.46 (s, 3, 18-CH_3), 1.06 (d, 3,
J = 6.6 Hz, 6α-CH_3), 1.38 (s, 3, 21-CH_3), 2.89 (s, 6,
-N(CH_3)$_2$), 3.8-4.0 (m, 8, 3, 20-diethylene ketal-H),
15 4.19 (d, 1, J = 6.2 Hz, 11α-H), 6.62 (d, 2, J = 8.8 Hz,
aromatic H _ortho_ to -N(CH_3)$_2$), 7.06 (d, 2, J = 8.8 Hz,
aromatic-H, meta to -N(CH_3)$_2$); Calcd for $C_{33}H_{47}O_6N$:   C,
71.58; H, 8.56; N, 2.53. Found: C, 71.70; H, 8.59; N,
2.51.

20   Phosphoric acid (85%, 6.5 mL) was added dropwise
into acetic anhydride (18 mL) in an ice-bath. The
mixture was stirred at 5-10°C for 30 min and diluted
with acetic acid (20 mL). The resulting mixture was
warmed to room temperature and stirred for 1 hour. The
25 above 17α-hydroxy-3,20-diketal (680 mg, 1.52 mmol) in
dry dioxane (4.0 mL) was added to the phosphoric
acid/acetic anhydride/acetic acid solution (8.0 mL).
The mixture turned immediately into a dark-blue
solution. The progress of the acetylation was
30 carefully monitored with reverse phase-HPLC analyses.
The reaction was stirred at room temperature for 8
hours and diluted with water followed by neutralization
with sodium bicarbonate solution (5% w/v). The product
was extracted with ethyl acetate (200 mL x 3). The

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organic phase was dried over sodium sulfate
(anhydrous), filtered and concentrated to give 750 mg
of crude reaction product which was purified by Al_2O_3
column chromatography followed by repeated reverse-
5 phase column chromatography employing a RP-C8 (Lobar
size B) column and 20% H_2O in MeOH as the eluting
solvent system. Each individual fraction collected was
monitored by an analytical Zorbax-ODS (4.5 mm x 25 cm)
column with the same solvent system. The fractions
10 showing greater than 95% purity were combined and
solvent was evaporated. Further recrystallization from
MeOH/H_2O provided 110 mg of white crystals of 6α-
methyl-17α-acetoxy-11β-(4-N,N-dimethylaminophenyl)-19-
norpregna-4,9-diene-3,20-dione. The major contaminant
15 found both in the mother liquor and in the overlapping
fractions was the 6β-methyl isomer. For the 6α-methyl
isomer: mp=189-190.5°C; ^1H NMR (250 MHz, $CDCl_3$) δ 0.35
(s, 3, 18-CH_3), 1.24 (d, 3, J = 6.5 Hz, 6α-CH_3), 2.09
(s, 3, 17α-OAc), 2.12 (s, 3, 21-CH_3), 2.9 (s, 6,
20 -N(CH_3)$_2$), 4.40 (d, 1, J = 7.2 Hz, 11α-H), 5.89 (bs, 1,
4-H), 6.62 (d, 2, J = 8.8 Hz aromatic-H, ortho to
-N(CH_3)$_2$), 6.96 (d, 2, J = 8.8 Hz aromatic-H, meta to
-N(CH_3)$_2$); Calcd mass for $C_{31}H_{39}O_4N$: 489.2879. Found
489.2878; IR ($CHCl_3$), 1730 (17α-C=O), 1720 (20-C=O),
25 1655 (conjugated 3-C=O) cm^{-1}; UV (MeOH) λ_{max} 302 nm
(dienone), 264 nm (aromatic group); Anal. calcd for
$C_{31}H_{39}O_4N$: C, 76.04; H, 8.02; N, 2.86. Found: C,
76.10; H, 8.03; N, 2.84.

Example 2. Synthesis of 17α-Acetoxy-11β-(4-N,N-
30 dimethylaminophenyl)-19-norpregna-4,9-diene-3,20-dione

3-Methoxy-19-norpregna-1,3,5(10),17(20)-tetraene
(Krubiner and Oliveto, 1966) (1.0 g, 0.0034 mol) in dry
pyridine (15 mL) was treated with osmium tetroxide

(1.0 g). The resulting dark brown solution was stirred
at room temperature for 2 hours and a solution of
sodium bisulfite (1.8 g in 30 mL H_2O) and pyridine (20
mL) was added and the mixture was stirred for an
5 additional 15 min.

The product was extracted with ethyl acetate and
the combined organic phase was washed with water, dried
over sodium sulfate (anhydrous), filtered and
concentrated. Flash chromatography (SiO$_2$; 10% acetone
10 in CH_2Cl_2) provided 0.82 g of 3-methoxy-19-norpregna-
1,3,5(10)-triene-17α,20α-diol: ^{1}H NMR (CDCl$_3$, 250 mHz)
δ 0.76 (s, 3, 18-CH$_3$), 1.23 (d, 3, J = 6.3 Hz, 21-H),
3.77 (s, 3, OMe), 3.87 (q, 1, J = 6.3 Hz, 20-H), 6.62
(d, 1, J = 2.8 Hz. 4-H), 6.70 (dd, 1, J = 8.5. 2.8 Hz,
15 2-H), 7.20 (d, 1, J = 8.5 Hz, 1-H).

By reduction with lithium in ammonia followed by
oxalic acid treatment as described in Example 1, the
above methyl ether (760 mg) was converted to 3-methoxy-
19-norpregna-2,5(10)-diene-17α,20α-diol and thence to
20 17α,20α-dihydroxy-19-nor-5(10)-pregnen-3-one. ^{1}H NMR
(90 MHz, CDCl$_3$), δ 0.80 (s, 3, 18-CH$_3$), 1.2 (d, 3, J =
6.5 Hz. 21-H), 2.4 (bs, 2, 4-H), 4.0 (m, 1, 20-H).

Pyridinium hydrobromide perbromide (1.5 mmol) as
in Example 1, converted this compound to 230 mg of
25 17α,20(α)-dihydroxy-19-norpregna-4,9-dien-3-one. [1]H
NMR (CDCl$_3$, 90 MHz) δ 0.95 (s, 3, 18-CH$_3$), 1.15 (d, 3,
J = 6.5 Hz, 21-H), 4.1 (m, 1, 20-H), 5.7 (s, 1, 4-H).

Oxidation of the above diol (210 mg) with oxalyl
chloride and dimethylsulfoxide as in Example 1 gave
30 17α-hydroxy-19-norpregna-4,9-diene-3,20-dione: ^{1}H NMR
(CDCl$_3$, 90 MHz) δ 0.87 (s, 3, 18-CH$_3$), 2.25 (s, 3, 21-
H), 5.70 (bs, 1, 4-H); IR (CHCl$_3$) 1700 (20-C=O), 1665
(conjugated 3-C=O) cm^{-1}. This compound was converted

to 190 mg of 3,3,20,20-bis-(ethylenedioxy)-19-
norpregna-5(10),9(11)-dien-17α-ol by the procedure
described in Example 1: ^{1}H NMR (CDCl$_3$, 90 MHz) δ 1.35
(s, 3, 21-H), 0.80 (s, 3, 18-CH$_3$), 3.98 (m, 8, 3,20-
5   ketals), 5.6 (bs, 1, 11-H).

The above bisketal (175 mg) was epoxidized with
meta-chloroperbenzoic acid by the procedure of Example
1 to yield crude 5α,10α-epoxy-3,3,20,20-bis-
(ethylenedioxy)-19-norpregn-9(11)-en-17α-ol (25) which
10   underwent copper catalyzed Grignard addition as in
Example 1 to provide 100 mg of 3,3,20,20-
bis(ethylenedioxy)-11β-(4,N,N-dimethylaminophenyl)-19-
norpregn-9-ene-5α,17α-diol: ^{1}H NMR (CDCl$_3$, 90 MHz)
δ0.46 (s, 3, 18-CH$_3$), 1.38 (s, 3, 21-H), 2.89 (s, 6,
15   -N(CH$_3$)$_2$), 3.8 (m, 8, 3,20-ketals), 4.78 (bt, 1, 11α-
H), 6.6-7.1 (m, 4, aromatic-H).

Treatment of this compound with acetic
anhydride/phosphoric acid as described in Example 1
yielded 17α-acetoxy-11β-(4-N,N-dimethylaminophenyl)-19-
20   norpregna-4,9-diene-3,20-dione which was recrystallized
from MeOH/H$_2$O to give 25 mg of the final product:
mp=118-121°C; ^{1}H NMR (CDCl$_3$, 250 MHz) δ 0.36 (s, 3, 18-
CH$_3$), 2.09 (s, 3, 17α-OAc), 2.13 (s, 3, 21-CH$_3$), 2.9
(s, 6, -N(CH$_3$)$_2$), 4.39 (d, 1 J = 7.0 Hz, 11α-H), 5.77
25   (s, 1, 4-H), 6.6 (d, 2, J = 8.6 Hz, aromatic ortho-H to
-N(CH$_3$)$_2$), 6.9 (d, 2, J = 8.6 Hz, aromatic meta-H to
N(CH$_3$)$_2$; IR (CHCl$_3$) 1730 (20-C=O), 1660 (3-conjugated
C=O) cm^{-1}; UV (MeOH), λ$_{max}$, 261 nm; Anal. Calcd. for
C$_{30}$H$_{37}$NO$_4$:   C, 75.76; H, 7.84; N, 2.94.   Found: C,
30   74.18; H, 7.75; N, 2.81.

Example 3.   Synthesis of 6α-Methyl-16α-ethyl-11β-(4-
N,N-dimethylaminophenyl)-19-norpregna-4,9-diene-3,20-
dione.

6α-Methyl-3-methoxy-19-norpregna-1,3,5(10)-triene-17α,20β-diol (900 mg, 2.6 mmol) in 30 mL of THF was treated with H_5IO_6 solution (400 mg in 10 mL THF). The reaction mixture was stirred at room temperature for 45

5 min and filtered through a short neutral alumina column. The filtrate and THF washings were combined and concentrated to give 750 mg of product. Recrystallization from methanol gave 450 mg of 3-methoxy-6α-methyl-1,3,5(10)estratrien-17-one: mp=108-

10 109°C; ^{1}H NMR (CDCl$_3$, 90 MHz) δ 0.88 (s, 3, 18-CH$_3$), 1.3 (d, 3, J = 6.5 Hz, 6α-Me), 3.75 (s, 3, 3-OMe), 6.8-7.2 (m, 3, aromatic H); IR (CHCl$_3$) 1740 cm^{-1} (17-C=O); Anal. calcd for $C_{20}H_{26}O_2$: C, 80.5; H, 8.78. Found: C, 80.59; H. 8.80.

15 A solution of the above 6α-methylestrone-3-methyl ether (5.2 g. 0.017 mol) in dry toluene was added rapidly to a stirred solution of ethylidenetriphenylphosphorane freshly prepared from 6.3 g of NaH in 100 mL of DMSO and

20 ethyltriphenylphosphonium iodide (54.8 g, 0.13 mol). The reaction mixture was stirred at 60°C for 18 hours and was then poured over ice. The product was taken up with ethyl acetate. The combined organic phase was dried over sodium sulfate, filtered, and concentrated

25 to give 8.5 g of crude product which was purified by SiO$_2$ column chromatography (hexane - CH$_2$Cl$_2$, 1:1) to give 4.8 g of 3-methoxy-6α-methyl-19-norpregna-1,3,5(10),17(20)-tetraene. ^{1}H NMR (CDCl$_3$, 90 MHz) δ 0.89 (s, 3, 18-CH$_3$): 1.3 (d, 3, J = 6.5 Hz, 6α-

30 CH$_3$), 1.6 (d, 3, J = 7 Hz, 21-H), 3.8 (s, 3, OMe), 5.1 (m, 1, 20-H), 6.8-7.2 (m, 3, aromatic-H); IR (CHCl$_3$), no C=O.

A solution of the above olefin (500 mg, 1.61 mmol) and hematoporphyrin (22 mg) in 20 mL of pyridine was

treated with a fine stream of oxygen while being
illuminated with a 22 W fluorescent lamp. After 4.5 h,
5 mL of acetic anhydride was added and the reaction
mixture was allowed to stand at room temperature for 45
5   min and was then heated at 60°C for additional 30
min. After dilution with water, the product was
extracted with methylene chloride and the organic phase
washed thoroughly with 1N HCl and then with 5% sodium
bicarbonate solution. After drying, the methylene
10   chloride solution was slurried with 15 g of neutral
alumina oxide and filtered. The concentrated crude
reaction product was further purified by SiO_2 column
chromatography (15% acetone in CH_2Cl_2) to provide 350
mg of 3-methoxy-6α-methyl-19-norpregna-1,3,5(10),16-
15   tetraen-20-one: mp=106-109°C; ^1H NMR ($CDCl_3$, 90 MHz),
δ 0.90 (s, 3, 18-CH_3), 1.29 (d, 3, J = 6.5 Hz, 6α-CH_3),
2.23 (s, 3, 21-H), 3.75 (s, 3, OMe), 6.7 (m, 3, 2, 4 &
16-H), 7.15 (d, 1, J = 7 Hz, 1-H): IR ($CHCl_3$) 1670
(conjugated 20-C=O) cm^{-1}.

20   Ethylmagnesium bromide (12.5 mL, 25 mmol) 2 M in
THF was added to a suspension of $Me_2S \cdot CuBr$ complex (2.4
g, 0.0177 mol) in 80 mL of THF at 0°C under N_2. The
resulting blue solution of the complex was stirred at
0°C for 20 min and then was added to a cold solution of
25   the above tetraene (1.5 g, 0.0046 mol) in 40 mL of
THF. The reaction mixture was stirred for 30 min at
0°C and then diluted with 1 N HCl solution (15 mL).
The product was extracted with ethyl acetate. The
organic phase was dried, filtered and concentrated to
30   give 2.0 g of crude reaction product. Column
chromatography (SiO_2; 2% acetone in CH_2Cl_2) provided
1.5 g of 3-methoxy-6α-methyl-16α-ethyl-19-norpregna-
1,3,5(10)-trien-20-one; ^1H NMR ($CDCl_3$, 250 MHz) δ 7.18
(d, 1, J = 8.6 Hz, 1-H), 6.75 (m, 2, 2 & 4-H), 3.78 (s,

3, OMe), 2.15 (s, 3, 21-H), 1.30 (d, 3, J = 6.8 Hz, 6α-CH$_3$), 0.85 (t, 3, J = 7 Hz, 16-CH$_2$CH$_3$), 0.65 (s, 3, 18-CH$_3$); IR (CHCl$_3$) 1702 (20-C=O) cm^{-1}.

5   The above 20-keto compound (7.0 g, 0.020 mol) in THF (250 mL) and methanol (80 mL) was cooled to 0°C in an ice bath and treated with sodium borohydride (1.0 g, 0.027 mol). The mixture was stirred at 0°C for 6.5 hours and was then poured carefully into crushed ice. The product was extracted with ethyl acetate. The

10   organic extract was dried, filtered and concentrated to give 7.3 g of crude product which was purified by SiO$_2$ column chromatography (2% acetone in CH$_2$Cl$_2$) to provide 6.8 g of 3-methoxy-6α-methyl-16α-ethyl-19-norpregna-1,3,5(10)-trien-20β(α)-ol: ^{1}H NMR (CDCl$_3$, 250

15   MHz) δ 0.82 (s, 3, 18-CH$_3$), 0.90 (t, 3, J = 7.2 Hz, 16-CH$_2$CH$_3$), 1.22 (d, 3, J = 6.3 Hz, 6α-CH$_3$), 1.30 (d, 3, J = 6.8 Hz, 21-H), 2.9 (m, 1, 20-H), 3.78 (s, 3, 3-OMe), 6.7 (dd, 1, J = 8.5, 2.7 Hz, 2-H), 6.8 (d, 1, J = 2.7 Hz, 4-H), 7.20 (d, 1, J = 8.5 Hz, 1-H).

20   By the lithium in liquid ammonia procedure of Example 1, the above steroid (4.0 g. 0.0113 mol) was converted to 3.95 g of crude 3-methoxy-6α-methyl-16α-ethyl-19-norpregna-2,5(10)-dien-20β(α)-ol which upon treatment with oxalic acid by the procedure in Example

25   1 provided 2.85 g of 6α-methyl-16α-ethyl-20β(α)-hydroxy-19-nor-5(10)-pregnen-3-one: ^{1}H NMR (CDCl$_3$, 250 MHz) δ 0.82 (s, 3, 18-CH$_3$), 0.89 (t, 3, J = 7.0 Hz, 16-CH$_2$CH$_3$), 1.0 (d, 3, J = 6.9 Hz, 6α-CH$_3$), 1.20 (d, 3, J = 6.2 Hz, 21-H), 3.8 (m, 1, 20-H).

30   Treatment of the latter (220 mg) with pyridinium hydrobromide perbromide by the procedure of Example 1 provided 22 mg of 20α-isomer and 150 mg of 20β-isomer of 20-hydroxy-6α-methyl-16α-ethyl-19-norpregna-4,9-dien-3-one. For 20β-ol; ^{1}H NMR (CDCl$_3$, 250 MHz) δ 0.88

(t, 3, J = 7.0 Hz, 16-CH_2CH_3), 0.97 (s, 3, 18-CH_3),
1.15 (d, 3, J =6.5 Hz, 6α-CH_3), 1.22 (d, 3, J = 6.2 Hz,
21-H), 3.8 (m, 1, 20-H), 5.8 (s, 1, 4-H): IR ($CHCl_3$)
3400 (-OH), 1660 (conjugated 3-C=O), cm^{-1}; Anal. Calcd.

5   for $C_{23}H_{34}O_2$: C, 80.65; H. 10.00. Found: C, 79.36;
H, 9.95. For 20α-ol: ^{1}H NMR ($CDCl_3$, 250 MHz),
δ 0.86 (s, 3, 18-CH_3), 0.91 (t, 3, J = 7.2 Hz, 16-
CH_2CH_3), 1.15 (d, 3, J = 6.5 Hz, 6α-CH_3), 1.26 (d, 3,
J = 6.2 Hz, 21-H), 3.8 (m, 1, 20-H), 5.8 (s, 1, 4-H).

10   Oxidation of the above 20-ol (230 mg) with oxalyl
chloride and dimethylsulfoxide by the procedure in
Example 1 afforded 165 mg of 6α-methyl-16α-ethyl-19-
norpregna-4,9-diene-3,20-dione: mp=118-119°C; ^{1}H NMR
($CDCl_3$, 250 MHz), δ 0.80 (s, 3, 18-CH_3), 0.82 (t, 3, J

15 =7.1 Hz, 16-CH_2CH_3), 1.15 (d, 3, 6.5 Hz, 6α-CH_3), 2.15
(s, 3, 21-H), 5.8 (s, 1, 4-H): IR ($CHCl_3$), 1705 (20-
C=O), 1665 (conjugated 3-C=O) cm^{-1}; Anal. calcd. for
$C_{23}H_{32}O_2$: C, 81.13; H, 9.47. Found: C, 81.01;
H, 9.48.

20   This latter compound (410 mg, 1.2 mmol) was
converted with ethylene glycol and p-toluenesulfonic
acid by the procedure of Example 1 to 3,3,20,20-bis-
(ethylenedioxy)-6α-methyl-16α-ethyl-19-norpregna-
5(10),9(11)-diene (320 mg): ^{1}H NMR ($CDCl_3$, 90 MHz)

25 δ 0.80 (s, 3, 18-CH_3), 0.85 (t, 3, J = 7 Hz, 16-
CH_2CH_3), 1.1 (d, 3, J = 6.5 Hz, 6α-CH_3), 2.1 (s, 3, 21-
H), 3.8-4.0 (m, 8, 3,20-ketals), 5.5 (bs, 1, 11-H).

      Epoxidation of the bisketal (305 mg. 0.71 mmol)
with m-chloroperbenzoic acid (220 mg, 1.28 mmol)
30 followed by the copper catalyzed Grignard addition
procedure of Example 1 gave 1.2 g of dark blue residue
containing 3,3,20,20-(ethylenedioxy)-6α-methyl-16α-
ethyl-11β-(4-N,N-dimethylaminophenyl)-19-nor-9-pregnen-
5α-ol.

Without further purification, the above material
was treated with 70% aqueous acetic acid and then
heated at 50°C for 40 min. The reaction mixture was
poured into ice water and neutralized with 10% (w/v)
5   NaHCO$_3$ solution. The product was extracted with
CH$_2$Cl$_2$, dried over sodium sulfate (anhydrous), filtered
and concentrated to give 240 mg of dark blue solid.
Column chromatography (SiO$_2$; 5% acetone-CH$_2$Cl$_2$)
provided 42 mg of a single spot (TLC) material. An
10 HPLC analysis (Zorbax-ODS 4.6 mm x 25 cm. 15% H$_2$O in
MeOH) showed that the product consisted of 6α and 6β-
methyl isomers in an approximate ratio of 2:1. A
preparative Rp-C18 column chromatography (20% H$_2$O in
MeOH) provided 7.0 mg of 6α-methyl-16α-ethyl-11β-(4-
15 N,N-dimethylaminophenyl)-19-norpregna-4,9-diene-3,20-
dione and 2.5 mg of 6β-methyl-16α-ethyl-11β-(4-N,N-
dimethylaminophenyl)-19-norpregna-4,9-diene-3,20-dione,
together with 15 mg of unresolved mixture. For 6α-
methyl compound: mp=95-98°C; ^{1}H NMR (CDCl$_3$, 250
20 MHz) δ 0.36 (s, 3, 18-CH$_3$), 0.82 (t, 3, J = 7.2 Hz, 16-
CH$_2$CH$_3$), 1.22 (d, 3, J = 6.5 Hz, 6α-CH$_3$), 2.16 (s, 3,
21-H), 2.9 (s, 6, N(CH$_3$)$_2$), 4.32 (d, 1, J = 6.7 Hz,
11α-H), 5.88 (s, 1, 4-H), 6.6 (d, 2, J = 8.7 Hz,
aromatic-H ortho to N(CH$_3$)$_2$), 6.98 (d, 2, J = 8.7 Hz,
25 aromatic-H meta to N(CH$_3$)$_2$). IR (CHCl$_3$) 1702 (20-C=O),
1660 (conjugated 3-C=O) cm^1; UV (MeOH)
λ$_{max}$ 301, 260 nm; MS calcd. 459.3137. Found:
459.3141; Anal. calcd. for C$_{31}$H$_{41}$NO$_2$; C, 80.99; H,
8.92; N, 3.04. Found: C, 80.18; H, 9.02; N, 2.94.
30 For the 6β-methyl isomer: ^{1}H NMR (CDCl$_3$, 250
MHz) δ 0.39 (s, 3, 18-CH$_3$), 0.82 (t, 3, J = 7.2 Hz, 16-
CH$_2$CH$_3$), 1.28 (d, 3, J = 7.1 Hz, 6β-CH$_3$), 2.17 (s, 3,
21-H), 2.9 (s, 6, N(CH$_3$)$_2$), 4.33 (d, 1, J = 6.7 Hz,
11α-H), 5.78 (s, 1, 4-H), 6.6 (d, 2, J = 8.7 Hz,
35 aromatic-H ortho to N(CH$_3$)$_2$), 6.98 (d, 2, J = 8.7 Hz,

aromatic-H meta to $-N(CH_3)_2$.

Example 4.   Synthesis of 16α-Ethyl-11β-(4-N,N-dimethylaminophenyl)-19-norpregna-4,9-diene-3,20-dione.

A solution of sodium hydride (0.27 g, 11.3 mmol)
5   in anhydrous dimethyl sulfoxide (15 mL) was heated at
75°C for 1 hour. The reaction mixture was then cooled
to room temperature and a solution of ethyl
triphenylphosphonium iodide (4.6 g, 11.3 mmol) in
dimethyl sulfoxide (10 mL) was slowly added. After
10   stirring at room temperature for 15 min, a solution of
3,3-ethylenedioxy-11β-(4-N,N-dimethylaminophenyl-5α-
hydroxyestr-9-en-17-one (prepared according to Cook et
al, U.S. patent application serial no. 908,288 (1.0 g,
2.2 mmol) in anhydrous toluene (25 mL) was added
15   dropwise, and the reaction mixture was subsequently
heated at 80°C for 2 hours. The solution was
cautiously poured into ice water (250 mL) and extracted
with methylene chloride (3 x 150 mL). The combined
extracts were washed with water (2 x 50 mL) and
20   brine. Removal of the dried (Na_2SO_4) solvent in vacuo
yielded the crude product which was purified by elution
from silica gel (50 g) using 1:1 ether-hexane
containing 0.1% Et_3N to give 0.69 g (68%) of 3,3-
ethylenedioxy-11β-(4-N,N-dimethylaminophenyl)-19-
25   norpregna-9,17(20)-dien-5α-ol: mp=174-177°C; IR
($CHCl_3$) 3600 cm^{-1}; ^1H NMR (250 MHz, $CDCl_3$) δ 0.56 (s,
3, 18-H), 2.91 (s, 6, NMe_2), 3.98 (m, 4, OCH_2CH_2O),
4.19 (m, s, 11-H), 4.29 (s, 1, 5-OH), 5.08 (m, 1, 20-
H), 6.50 (d, J = 9 Hz, 2, ArH ortho to NMe_2), 7.09 (d,
30   J = 9 Hz, 2, ArH meta to NMe_2). Mass spectrum: m/z
required for $C_{30}H_{41}NO_3$: 463.3086. Found: 463.3085.
Anal. Calcd for $C_{30}H_{41}NO_3$: C, 77.71; H, 8.91; N,
3.02. Found: C, 77.45; H, 8.93; N, 2.95.

Oxygen gas was slowly bubbled through a solution
of the above olefin (0.33 g. 0.7 mmol) and
hematoporphyrin (15 mg) in pyridine (7 mL), while the
solution was irradiated with a fluorescent lamp (25 w)
5   placed 7 cm from the reaction flask. After 3 days, the
bubbling of oxygen was discontinued. To this reaction
mixture was then added acetic anhydride (3 mL), and the
solution stirred at room temperature for 2 hours. The
solvents were then removed in vacuo at room
10 temperature, and the residue eluted from silica gel (50
g) using 2% acetone in methylene chloride containing
0.1% Et_3N to give 140 mg of unchanged starting
material. Continued elution with 4% acetone in
methylene chloride containing 0.1% Et_3N yielded 3,3-
15 ethylenedioxy-11β-(4-N,N-dimethylaminophenyl)-5α-
hydroxy-19-norpregna-9,16-dien-20-one (55 mg, 30% based
on recovered starting material) as crystals; mp=225-
228°C; IR ($CHCl_3$) 3600, 1675 cm^{-1}; ^1H NMR (250 MHz,
$CDCl_3$) δ 0.59 (s, 3, 18-H), 2.24 (s, 3, 21-H), 2.90 (s,
20 6, NMe_2), 3.98 (m, 4, OCH_2CH_2O), 4.18 (m, 1, 11-H),
4.37 (s, 1, 5-OH), 6.65 (d, J = 9 Hz, 2, ArH ortho to
NMe_2), 6.67 (apparent s, 1, 16-H), 7.10 (d, J = 9 Hz,
1, ArH meta to NMe_2). Mass spectrum: m/z required for
$C_{30}H_{39}NO_4$ (M^+-18); 459.2773. Found: 459.2774. Anal.
25 Calcd for $C_{30}H_{39}NO_4$ • 1/4 H_2O: C, 74.88; H, 8.24; N,
2.90. Found: C, 74.72; H, 8.31; N, 2.86.

To a cold (0°C), stirred suspension of copper
bromide-dimethyl sulfide complex (120 mg, 0.58 mmol) in
anhydrous tetrahydrofuran (1 mL) was slowly added 0.4
30 mL (2.0 molar, 0.8 mmol) of ethylmagnesium bromide in
tetrahydrofuran. After stirring at 0° for 0.5 h, the
Grignard complex was rapidly added to a cold (0°C),
stirred solution of the above unsaturated ketone (16
mg, 0.034 mmol) in tetrahydrofuran (0.5 mL). After

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stirring at 0°C for 2 h, the reaction mixture was added
dropwise to a cold (0°C), rapidly stirred solution of 3
N hydrochloric acid (1 mL). After stirring at room
temperature for 2 h, the mixture was poured into a
5   saturated solution of sodium bicarbonate (10 mL) and
extracted with ethyl acetate (3 x 25 mL). The combined
extracts were washed with water (2 x 50 mL) and
brine. Removal of the dried (Na_2SO_4) solvent in vacuo
yielded the crude product which was purified by elution
10 from a reverse phase C-8 column (size B, E. M. Merck)
using 85% aqueous methanol to yield 11 mg (80%) of
16α-ethyl-11β-(4-N,N-dimethylaminophenyl)-19-norpregna-
4,9-diene-3,20-dione as off-white crystals;
mp=168-171°C; IR ($CHCl_3$) 1720, 1680 cm^{-1}; ^1H NMR (250
15 MHz, $CDCl_3$) δ 0.36 (s, 3, 18-H), 0.82 (t, 3, J = 7 Hz,
CH_2CH_3), 2.16 (s, 3, 21-H), 2.91 (s, 6, NMe_2), 4.32 (m,
1, 11-H), 5.76 (s, 1, 4-H), 6.64 (d, J = 9 Hz, 2, ArH
ortho to NMe_2), 6.98 (d, J = 9 Hz, 2, ArH meta to
NMe_2). Mass spectrum: m/z required for $C_{30}H_{39}NO_2$;
20 445.2981. Found: 445.2977. Anal. Calcd for
$C_{30}H_{39}NO_2$:   C, 80.85 H, 8.82; N, 3.14.   Found: C,
80.75; H, 8.85; N, 3.09.

    Example 5, Synthesis of 11β-(4-N,N-
Dimethylaminophenyl)-19-norpregna-4,9,16-triene-3,20-
25 dione.

        To a cold (0°C) stirred solution of hydrochloric
acid (3 N, 1 mL) was slowly added a solution of 3,3-
ethylenedioxy-11β-(4-N,N-dimethylaminophenyl)-
5α-hydroxy-19-norpregna-5,16-dien-20-one (23 mg, 0.05
30 mmol) in tetrahydrofuran (2 mL). After being stirred
at room temperature for 2 h, the reaction mixture was
poured into a saturated solution of sodium bicarbonate
(10 mL) and extracted with methylene chloride (3 x 20
mL). The combined extracts were washed with water (2 x

20 mL) and brine. Removal of the dried (Na_2SO_4)
solvent in vacuo gave the crude product, which was
purified by elution from silica gel (0.5 g using 1%
acetone-methylene chloride containing 0.1% Et_3N) to

5 yield 12 mg (50%) of 11β-(4-N,N-dimethylaminophenyl)-
19-norpregna-4,9,16-triene-3,20-dione as a foam; IR
($CHCl_3$) 1675 cm^{-1}; ^{1}H NMR (250 MHz, $CDCl_3$) δ 0.66 (s,
3, 18-H), 2.26 (s, 3, 21-H), 2.91 (s, 6, NMe_2), 4.28
(m, 1, 11-H), 5.75 (s, 1, 4-H), 6.60 (d, J = 9 Hz, 2,

10 ArH ortho to NMe_2), 6.68 (apparent s, 1, 16-H), 7.06
(d, J = 9 Hz, 2, ArH meta to NMe_2). Mass spectrum:
m/z required for $C_{28}H_{33}NO_2$; 415.2511. Found:
415.2513.

   Example 6. Synthesis of 11β-(4-N,N-

15 Dimethylaminophenyl)-19-norpregna-4,9-diene-3,20-dione.

      3,3-Ethylenedioxy-11β-(4-N,N-dimethylaminophenyl-
5α-hydroxy-19-norpregna-9,16-diene-3,20-dione in
ethanol solution was reduced with hydrogen in the
presence of 5% palladium on charcoal. After one mole

20 of hydrogen per mole of steroid was taken up, the
solution was filtered and treated with hydrochloric
acid in ethanol as described in Example 1. Evaporation
left a residue which was purified by chromatography to
yield 11β-(4-N,N-dimethylaminophenyl)-19-norpregna-4,9-

25 diene-3,20-dione.

   Example 7. Synthesis of 11β-(4-N,N-
Dimethylaminophenyl)-19-norpregna-4,9,17(20)-trien-3-
one.

      3,3-Ethylenedioxy-11β-(4-N,N-dimethylaminophenyl)-

30 19-norpregna-9,17(20)-dien-5α-ol was treated with
hydrochloric acid in ethanol as described in Example 1
and purified by chromatography to yield 11β-(4-N,N-
dimethylaminophenyl)-19-norpregna-4,9,17(20)-trien-3-

one.

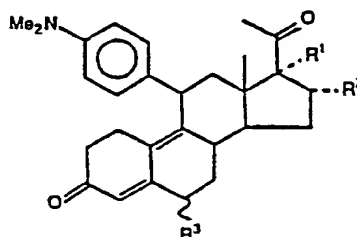Example 8. Synthesis of 11β-(4-acetylphenyl-19-norpregna-4,9,16-triene-3,20-dione.

By the procedure described in Example 1 for the

5   synthesis of 6α-methyl-11β-(4-N,N-dimethylaminophenyl)-3,3,20,20-bis(ethylenedioxy)-19-norpregn-9-ene-5α, 17α-diol from 6α-methyl-3,3,20,20-bis(ethylenedioxy)-19-norpregna-5(10),9(11)-dien-17α-ol, but substituting 2-(4-bromomagnesiumphenyl)-2,5,5-trimethyl-1,3-dioxane

10   for p-N,N-dimethylaminophenylmagnesium bromide, 3,3-(ethylenedioxy)estra-5(10),9(11)-dien-17-one was converted to 3,3-ethylenedioxy-5α-hydroxy-11β-[4-(2,5,5-trimethyl-1,3-dioxan-2-yl)phenyl]estr-9-en-17-one. The latter compound was subjected to the

15   procedures of Example 4 for converting 3,3-ethylenedioxy-11β-(4-N,N-dimethylaminophenyl)-5α-hydroxy-9-estren-17-one to 3,3-ethylenedioxy-11β-(4-N,N-dimethylaminophenyl)-5α-hydroxy-19-norpregna-9,16-dien-20-one followed by acid hydrolysis as described in

20   Example 5 to yield 11β-(4-acetylphenyl)-19-norpregna-4,9,16-triene-3,20-dione, m.p. around 194-197°C. Mass spectrum: m/z required for $C_{28}H_{30}O_3$: 414.2195. Found: 414.2189.

Example 9. In Vitro Binding to Receptors

25   The in vitro activity of the subject compounds was determined by measuring the binding affinities (RBA) of these compounds relative to progesterone for the progesterone receptor in the cytosol obtained from estrogen-primed immature rabbit uterus and by measuring

30   the RBA relative to dexamethasone for the glucocorticoid receptor from thymus of adrenalectomized rats. These assays were carried out by the procedures of J.R. Reel et al., Fertility and Sterility, 31, 552 (1979) (progesterone) and G.P. Chrousos et al.,

Endocrinology, 107, 472 (1980) (glucocorticoid). The
results are presented in Table 1.

TABLE I
RELATIVE RECEPTOR BINDING ACTIVITY

	Compound			Progestin RBA[a]	Glucocort. RBA[b]	P-RBA/G-RBA[c]
	R_1	R_2	R_3			
	—OAc	—H	—H	47	198	0.24
	—OAc	—H	α—CH$_3$	43	242	0.18
	—OAc	—H	ß—CH$_3$	15	ND	—
	—OH	—H	—H	15	41	0.37
	—OH	—H	α—CH$_3$	46	175	0.26
	—H	—Et	—H	80	124	0.65
	—H	—Et	α—CH$_3$	61	246	0.42
	—H	—Et	ß—CH$_3$	48	106	0.45
	—— Δ^{16} ——		—H	8	ND	—

[a] Relative ability to displace tritium-labeled progesterone from the receptor in uterine cytosol from estrogen-primed immature female rabbits as compared with progesterone (= 100).
[b] Relative ability to displace tritium-labeled dexamethasone from the receptor of the thymus of adrenalectomized rats as compared to dexamethasone (= 100).
[c] Ratio of RBA values for progesterone receptor (P-RBA) to glucocorticoid receptor (G-RBA).

Example 10.   In Vivo Antiprogestational Activity

The antiprogestational activity of the compounds
was studied after both intrauterine and oral
administration.   In each case the compound was tested
5   for its ability to inhibit the endometrial response due
to subcutaneous administration of progesterone to
estrogen-primed immature female rabbits.   The
methodology used for the intrauterine test has been
described by D.A. McGinty et al.   See Endocrinology,
10   24, 829 (1939).   For oral administration of test
compounds, the method used was analogous to that of
Clauberg.   See Clauberg, Zentr. Gynakol., 54, 2757
(1930) as modified by McPhail J. Physiol. (London), 83,
145 (1935).

15   The results of the intrauterine tests are given in
Table 2.   Each active compound was characterized by a
dose-related ability to block the progestational effect
of simultaneously administered progesterone.   When the
percent inhibition was plotted versus the log of the
20   dose, linear relationships were obtained.   Linear
regression analysis permitted calculation of the ED_{50}
and ED_{90} values (the doses required for 50% and 90%
inhibition of the progesterone effect, respectively).
The actual dose which gave 90% or more inhibition is
25   also given, although this value is probably less
accurate than the calculated values which are based on
the dose-response line.   Very unexpectedly, these
results do not correlate well at all with the in vitro
binding studies.   Since the intrauterine administration
30   bypasses most of the drug-metabolizing systems of the
body, especially the liver, intrinsic activity is
expected to correlate reasonably well with binding
activity to the receptor, according to currently held
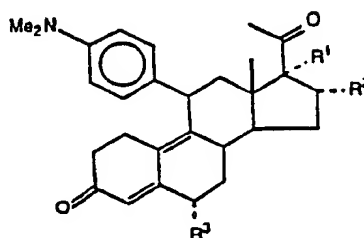hypotheses regarding receptor binding.   However

although the 17α-acetoxy compounds bind well and also
exhibit potent antiprogestational activity, the Δ-16
compound had even more potent activity even though its
RBA was less than one-fifth of the value of the

5 17α-acetoxy compounds. Even more surprising was the
lack of antiprogestational activity of the 16α-ethyl
compounds, even though they exhibited the strongest
binding to the progesterone receptor.

The 17α-acetoxy compounds also exhibited strong
10 antiprogestational activity when given by the oral
route, as is shown in Table 3 for 17α-acetoxy-6α-
methyl-11β-(4-N,N-dimethylaminophenyl)-19-norpregna-
4,9-diene-3,20-dione.

TABLE 2
SUMMARY OF ANTI-MCGINTY ACTIVITY

Compound				ED_{50} $(\mu g)^a$	ED_{90} $(\mu g)^a$	ED_{90} $(\mu g)^b$
	R_1	R_2	R_3			
8a	−OAc	−H	−H	0.41	1.2	2.0
8b	−OAc	−H	α−CH$_3$	0.54	1.9	2.0
19	−H	−Et	−H	—	—	>>80^c
15a	−H	−Et	α−CH$_3$	—	—	>>10^c
23		$-\Delta^{16}-$	−H	0.26^d	0.81^d	1.0^d
RU−486				0.28	0.87	1.0

[a] From % Inhib $= a + b \cdot \ln$ dose

[b] Actual dose giving $\geq 90\%$ inhibition

[c] No inhibition at tested dose

[d] Results variable. These data from "best run".

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TABLE 3

Oral Antiprogestational Activity
(Anti-Clauberg) of 17α-Acetoxy-6α-methyl-11β-
(4-N.N-dimethylaminophenyl)-19-nor-pregna-4.9-diene-3.20-dione (15)

$\underline{N}^a$	Total Oral Dose (mg)	Total SC Dose of Progesterone (mg)	Wt of Uterus (g ± SD)	McPhail Index (0-4)	% Inhibition[b]
6	0.0	0.0	1.98 ± 0.40	0	—
6	0.0	0.8	3.06 ± 0.45	3.96 ± 0.04	—
6	1.0	0.8	3.26 ± 0.34	3.46 ± 0.12	12.7 ± 3.0
6	5.0	0.8	2.14 ± 0.22	1.92 ± 0.48	51.6 ± 12.2
5	10.0	0.8	2.24 ± 0.27	1.30 ± 0.24	67.2 ± 6.1

a   Number of rabbits.

b   Based on change in McPhail Index.

TABLE 4
PROGESTATIONAL ACTIVITY
(MCGINTY ASSAY)
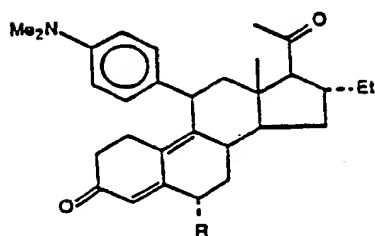
	R	Dose (ug)	McPhail Index	
			Right Horn (Control)	Left Horn (Treated)
5				
	−H	2.0	0	3.0 ± 0.32
		4.0	0	3.7 ± 0.12
10		8.0	0	3.6 ± 0.10
	α−CH$_3$	20.0	0	3.8 ± 0.12
		40.0	0	3.9 ± 0.12
		80.0	0	3.8 ± 0.12

Example 11.   Progestational Activity in Vivo

The 16α-ethyl compounds which showed no
antiprogestational activity were examined for
progestational activity in the intrauterine assay.   In
5   this assay estrogen-primed immature female rabbits are
treated by injection of the test compound into the left
horn of the uterus while the right horn is left
untreated as a control.   Each horn is then scored for
endometrial proliferation by the McPhail Index.   As
10   Table 4 shows, these compounds were potent
progestational agents.   This is a totally unexpected
result, since all examples of prior art known to the
inventors show that compounds which bind to the
progesterone reeptor and contain an 11β-(4-N,N-
15   dimethylaminophenyl)-substituent exhibit
antiprogestational activity.   It indicates a possible
need for reassessment of the current hypotheses
regarding the effect of this substituent on antagonist
versus agonist activity.

20   Obviously, numerous modifications and variations
of the present invention are possible in light of the
above teachings.   It is therefore to be understood that
within the scope of the present claims, the invention
may be practiced otherwise than as specifically
25   described herein.

Claims

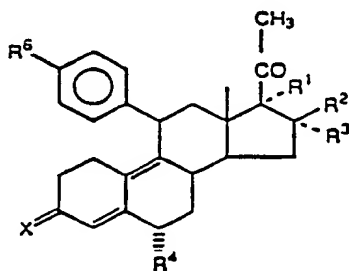1.   An 11β-aryl-19-norprogesterone steroid of the formula:
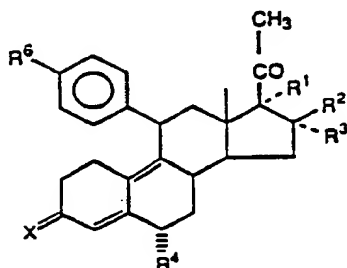
5   wherein (i) R^1 is H, C_{1-4} alkyl, C_{2-4} alkenyl, C_{2-4} alkynyl, OH, OC(O)CH$_3$, or OC(O)R^5, wherein R^5 is C_{2-8} alkyl, C_{2-8} alkenyl, C_{2-8} alkynyl or aryl, R_2 is H, R^3 is H, C_{1-4} alkyl, C_{2-4} alkenyl or C_{2-4} alkynyl, R^4 is H, CH$_3$, F or Cl, R^6 is H, (CH$_3$)$_2$N, CH$_3$O, CH$_3$CO, CH$_3$S,

10   CH$_3$SO, CH$_3$SO$_2$, and X is O or NOCH$_3$; or

      (ii) R^1 and R^2 taken together are a carbon-carbon bond and R^3, R^4, R^6 and X are as defined above; or

      (iii) R^1 and R^3 taken together are $-CH_2-$ or $-N=N-CH_2-$, R^2 is H and R^4, R^6 and X are as defined

15   above; or

      (iv) R^2 and R^3 taken together are $=CH_2$ and R^1, R^4, R^6 and X are as defined above in (i).

2.   The norprogesterone of Claim 1 of the formula:

20   wherein R^1 is H, C_{1-4} alkyl, C_{2-4} alkenyl, C_{2-4} alkynyl, OH, OC(O)CH$_3$, or OC(O)R^5, wherein R^5 is C_{2-8} alkyl, C_{2-8} alkenyl, C_{2-8} alkynyl or aryl, R_2 is H, R^3

is H, C_{1-4} alkyl, C_{2-4} alkenyl or C_{2-4} alkynyl, R^4 is
H, CH_3, F or Cl, R^6 is H, $(CH_3)_2N$, CH_3O, CH_3CO, CH_3S,,
CH_3SO, CH_3SO_2, and X is O or $NOCH_3$.

    3.   The norprogesterone of Claim 2, wherein R^6 is
5 N,N-dimethylamino or acetyl.

    4.   The norprogesterone of Claim 2, wherein R^4 is
hydrogen or methyl and R^1 is acetoxy or C_{2-8} alkynyl.

    5.   The norprogesterone of Claim 2, wherein said
norprogesterone is 17α-acetoxy-6α-methyl-11ß-(4-N,N-
10 dimethylaminophenyl)-19-norpregna-4,9-diene-3,20-dione,
17α-acetoxy-11ß-(4-N,N-dimethylaminophenyl)-19-
norpregna-4,9-diene-3,20-dione, 16α-ethyl-11ß-(4-N,N-
dimethylaminophenyl)-19-norpregna-4,9-diene-3,20-dione,
16α-ethyl-6α-methyl-11ß-(4-N,N-dimethylaminophenyl)-19-
15 norpregna-4,9-diene-3,20-dione, 17α-ethynyl-11ß-(4-N,N-
dimethylaminophenyl)-19-norpregna-4,9-diene-3,20-dione,
11ß-(4-N,N-dimethylaminophenyl)-19-norpregna-4,9-diene-
3,20-dione, 11ß-(4-acetylphenyl)-19-norpregna-4,9-
diene-3,20-dione, 17α-acetoxy-11ß-(4-acetylphenyl)-19-
20 norpregna-4,9-diene-3,20-dione, or 17α-ethynyl-11ß-(4-
acetylphenyl)-19-norpregna-4,9-diene-3,20-dione.

    6.   The norprogesterone of Claim 1, of the
formula:
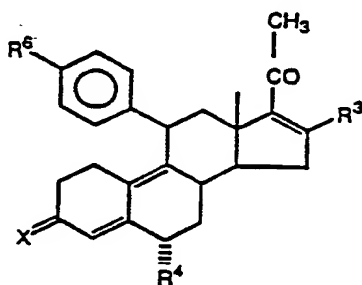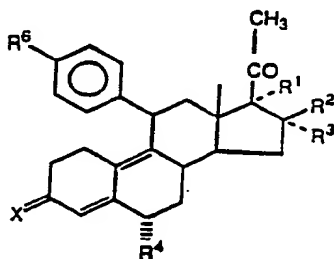

25 wherein R^3, R^4, R^6 and X are as defined in (i).

    7.   The norprogesterone of Claim 6, wherein R^6 is
N,N-dimethylamino or acetyl.

    8.   The norprogesterone of Claim 6, wherein said

norprogesterone is 11ß-(4-N,N-dimethylaminophenyl)-19-
norpregna-4,9,16-triene-3,20-dione or 11ß-(4-
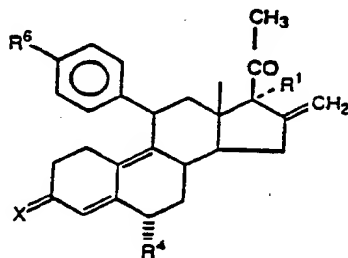acetylphenyl)-19-norpregna-4,9,16-triene-3,20-dione.

5   9.   The norprogesterone of Claim 1 having the
formula:

wherein R^1 and R^3 taken together are $-CH_2-$ or $-N=N-$
CH_2-, R^2 is H and R^4, R^6 and X are as defined in (i).

10.   The norprogesterone of Claim 9, wherein R^4 is
10 hydrogen or methyl and R^6 is dimethylamino or acetyl.

11.   The norprogesterone of Claim 1, having the
formula:

wherein R^1, R^4, R^6 and X are as defined in (i).

15   12.   The norprogesterone of Claim 11, wherein R^1
is acetoxy or C_{2-8} alkynyl, R^4 is hydrogen or methyl
and R^6 is dimethylamino or acetyl.

13.   A method of inducing an anti-glucocorticoid
antihormonal response, comprising administering to a
20 human or non-human mammal in need thereof, an anti-
glucocorticoid effective amount of a norprogesterone of
Claim 1, said norprogesterone having a binding affinity
for the glucocorticoid receptor and having anti-

glucocorticoid activity in said human or non-human mammal.

14. The method of Claim 13, wherein said effective amount is a unit dose between 0.1 milligram
5 and 1.0 gram.

15. The method of Claim 13, wherein said human or non-human mammal exhibits Cushing's syndrome or glaucoma.
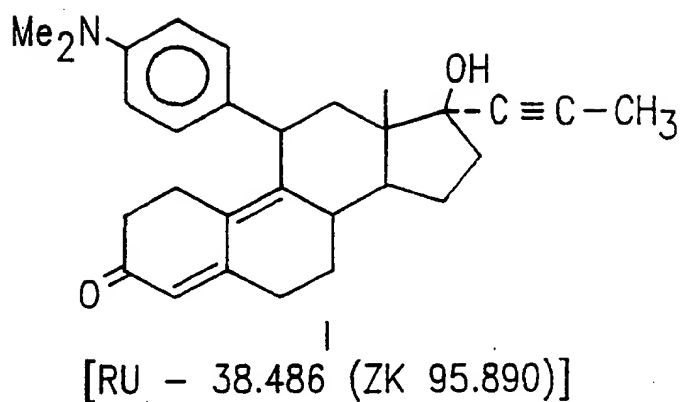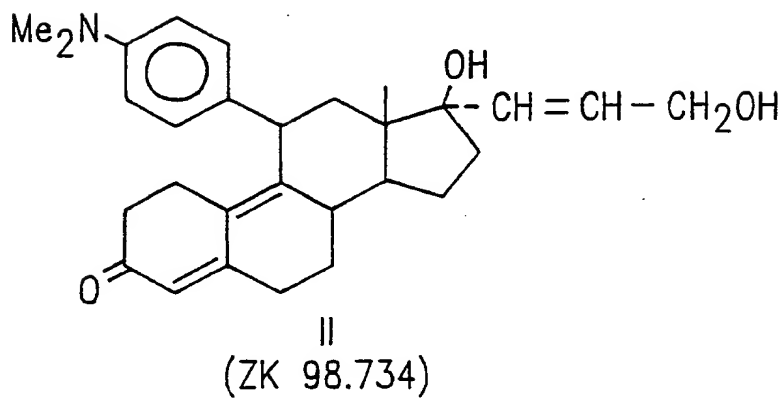
16. A method of inducing a progestational
10 hormonal response, comprising administering to a human or non-human mammal in need thereof, a progestional effective amount of a norprogesterone of Claim 1, said norprogesterone having a binding affinity for the progesterone receptor and possessing progestational
15 activity in said human or non-human mammal.

17. The method of Claim 16, wherein said effective amount is a unit dose between 0.1 milligram and 1.0 gram.

18. A method of inducing an anti-progestational
20 response in a human or non-human mammal, comprising administering to a human or non-human mammal in need thereof, an anti-progestational effective amount of a norprogesterone of Claim 1, said norprogesterone having a binding affinity for the progesterone receptor and
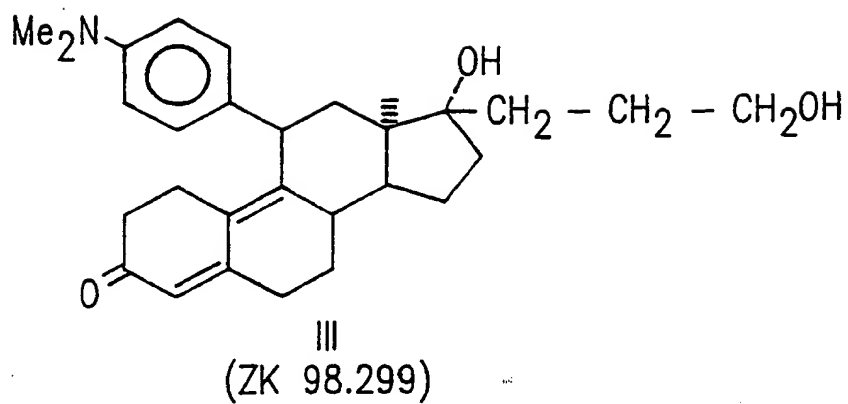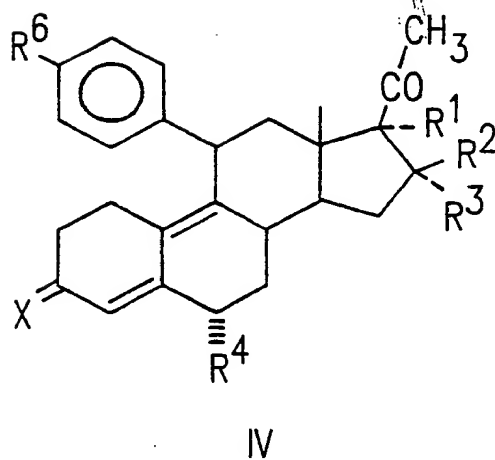25 possessing anti-progestational activity in said human or non-human mammal.

19. The method of Claim 18, wherein said effective amount is a unit dose between 0.1 milligram and 2.0 grams.

- 1 / 2 -

I
[RU - 38.486 (ZK 95.890)]

FIG. 1A

II
(ZK 98.734)

FIG. 1B

- 2 / 2 -

III
(ZK 98.299)

FIG. 1C

IV

FIG. 2

INTERNATIONAL SEARCH REPORT

I. CLASSIFICATION OF SUBJECT MATTER (if several classification symbols apply, indicate all) [6]

According to International Patent Classification (IPC) or to both National Classification and IPC

IPC(4): A61K 31/56, 31/58; C07J 1/00, 71/00
U.S.Cl.: 514/176,177,179,182; 260/397.3,397.45,397.5; 540/54

II. FIELDS SEARCHED

Minimum Documentation Searched [7]	
Classification System	Classification Symbols
U.S.	514/176, 177, 179, 182 540/54 260/397.3, 397.45, 397.5

Documentation Searched other than Minimum Documentation
to the Extent that such Documents are Included in the Fields Searched [8]

III. DOCUMENTS CONSIDERED TO BE RELEVANT [9]

Category [*]	Citation of Document, [11] with indication, where appropriate, of the relevant passages [12]	Relevant to Claim No. [13]
Y	US, A, 4,477,445 (PHILIBERT ET AL.) 16 October 1984, see abstract; col. 35, lines 57-58.	1,2,4, 13-15, 18,19
Y	US, A, 4,540,686 (PHILIBERT ET AL) 10 September 1985, see abstract; col. 25, line 55 - col 36, line 7.	1,2,4 13-15, 18,19

[*] Special categories of cited documents: [10]

"A" document defining the general state of the art which is not considered to be of particular relevance

"E" earlier document but published on or after the international filing date

"L" document which may throw doubts on priority claim(s) or which is cited to establish the publication date of another citation or other special reason (as specified)

"O" document referring to an oral disclosure, use, exhibition or other means

"P" document published prior to the international filing date but later than the priority date claimed

"T" later document published after the international filing date or priority date and not in conflict with the application but cited to understand the principle or theory underlying the invention

"X" document of particular relevance; the claimed invention cannot be considered novel or cannot be considered to involve an inventive step

"Y" document of particular relevance; the claimed invention cannot be considered to involve an inventive step when the document is combined with one or more other such documents, such combination being obvious to a person skilled in the art.

"&" document member of the same patent family

IV. CERTIFICATION

Date of the Actual Completion of the International Search	Date of Mailing of this International Search Report
12 SEPTEMBER 1989	27 SEP 1989
International Searching Authority	Signature of Authorized Officer
ISA/US	JOSEPH A. LIPOVSKY

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